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AN 2004-043117 [04] WPIDS

DNN N2004-034730 DNC C2004-017846

TI Mutated androgen receptor for constructing its expression cancer cells, applicable in diagnosis of cancer particularly (recurrent) prostate cancer and in developing and classifying antiandrogen drugs.

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NOVELTY - A method for constructing an antiandrogen-resistant cancer cell line that expresses a mutant androgen receptor is by culturing cancer cells sensitive to a specific androgen drug, in the presence of such drug, before analysis of the thus produced strains for mutation in the base sequence of the androgen receptor gene in these cells for selection.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

- (1) constructing an antiandrogen-resistant cancer cell line that expresses multiple mutant androgen receptor by expressing the mutant androgen receptor and culturing cancer cells sensitive to a specific androgen drug, in the presence of such drug, before analysis of the thus produced strains for mutation in the base sequence of the androgen receptor gene in these cells for selection;
- (2) cancer cell lines thus constructed;
- (3) screening antiandrogen agents by culturing any of the cancer cell lines in the presence of a test substance and investigating the antagonistic effect against expression of the mutant androgen receptor in such cells; or analysis of expression of the gene under the control of a promoter responsive to an androgen receptor in such cells;
- (4) antiandrogen agents with antagonistic effect against mutated androgen receptor thus screened;
- (5) screening antiandrogen agents for resistant cancer with non-inducibility or difficult inducibility by culturing an androgen-sensitive cell line, in the presence of a test substance, before chronologically investigating the appearance or none of proliferated cell line under these conditions;
- (6) antiandrogen agents for resistant cancer with (mutated) non-inducibility or difficult inducibility;
- (7) use of the antiandrogen agents for treating cancer;

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(8) kits for evaluating of responsiveness of the transcription factor of an androgen receptor to antiandrogen agents, or for screening androgen receptor modulators of the androgen receptor, containing mammalian cells with a gene under the regulation of a PSA promoter to enable expression analysis;

(9) screening modulators of the androgen receptor by contacting cells in the kits with a test substance before analysis of the gene expression;

(10) a protein containing an amino acid sequence identical with or substantially similar to:

(a) an amino acid sequence based on that of (11) of 924 amino acids but with the tryptophan at position-746 being substituted; or

(b) an amino acid sequence based on that of (11) but with the tryptophan at position-746 being substituted by leucine or cysteine and the threonine at position-882 substituted by alanine; or its salt;

(11) a partial peptide of the protein that contains a part of the amino acid sequence corresponding to the region in a normal androgen receptor necessary for binding with androgen, its amide, ester or their salt;

(12) a polynucleotide that encodes the protein or its partial peptide;

(13) diagnostics containing the polynucleotide;

(14) a recombinant vector containing the polynucleotide;

(15) a transformant containing the recombinant vector;

(16) animal cells capable of producing the protein;

(17) producing the protein, its partial peptide, their amide, ester or their salt by culturing the transformant or animal cells;

(18) screening compounds or their salts that can alter binding activity of the androgen with the protein, its partial peptide, their amide, ester or their salt by using them;

(19) a kit for screening compounds or their salts that can alter binding activity of the androgen with the protein, its partial peptide, their amide, ester or their salt containing them;

(20) preventives or remedies for hormone-sensitive cancer in the androgen-dependent and independent periods containing 2 or more antiandrogen agents with antagonistic effect against different mutated androgen receptors for combination;

(21) preventing or treating hormone-sensitive cancer in the androgen-dependent and independent periods by administering 2 or more antiandrogen agents with antagonistic effect against different mutated androgen receptors for combination into mammals;

(22) the use of these antiandrogen agents for producing preventives or remedies for hormone-sensitive cancer in the androgen-dependent and independent periods;

(23) an antibody recognizing the protein, its partial peptide, their amide, ester or their salt;

(24) diagnostics containing the antibody;

(25) compounds or their salts that can alter binding activity between androgen and e.g. the protein thus screened;

(26) drugs containing these screened compounds;

(27) quantifying mRNA that encodes the protein by using the polynucleotide or a part of it;

(28) quantifying the protein, its partial peptide, their amide, ester or their salt by using the antibody;

(29) diagnosis of metastasis of hormone-sensitive cancer in the androgen-dependent period by using any of the quantification methods;

(30) classifying antiandrogen agents by using the various types of in vitro mutated androgen receptor-expressing cell lines;

(31) preventives or remedies for hormone-sensitive cancer in the

androgen- dependent period containing a combination of not less than 2 of the thus classified antiandrogen agents;

(32) preventing or treating hormone-sensitive cancer in the androgen-dependent period by administering a combination of not less than 2 of the thus classified antiandrogen agents into mammals;

(33) the use of a combination of not less than 2 of the thus classified antiandrogen agents for producing preventives or remedies for hormone-sensitive cancer in the androgen-dependent period; and

(34) preventing or treating hormone-sensitive cancer in the androgen-independent period by administering the thus classified antiandrogen agents to mammals with onset of cancer resistant to an androgen drug due to its long-term use.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - None given in source material.

USE - The receptor is for constructing its expression cancer cells, both of which are applicable in diagnosis of cancer particularly (recurrent) prostate cancer and in developing and classifying antiandrogen drugs. With the mutated receptor, it is possible to diagnose recurrent prostate cancer early for treatment to greatly improve the survival rate and time of patients.

DESCRIPTION OF DRAWING(S) - A diagram showing the effect of vicaltamide on proliferation of LNCaP-cxD11, LNCaP-cxD2 and LNCaP-FGC cells: by suspending them at 40,000 cells/plate on RPMI 1640+10% DCC-FBS medium, in a 24-well plate; adding vicaltamide the day after sowing; and counting cells 3 days after vicaltamide addition. (Drawing includes non-English language text).

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